REMARKS

This Amendment responds to the Office Action mailed on December 28, 2007. In the Office Action, the PTO:

- rejected claims 13-20, 69-81 and 83-85 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Gosselin *et al.* (U.S. Patent No. 6,444,652) in combination with Weis *et al.* (WO 96/13512).

The pending claims are claims 13-20, 69-81 and 83-85. No new matter is added by this Amendment.

Response to Rejections Under 35 U.S.C. § 103(a)

Claims 13-20, 69-81 and 83-85 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gosselin *et al.* (U.S. Patent No. 6,444,652) in combination with Weis *et al.* (WO 96/13512).

The PTO alleged that Gosselin *et al.* in cols. 25-26 discloses **(1)** the reaction of silylated uracil with a protected ribose sugar to give the nucleoside 10 which is then deprotected according to the scheme in cols. 25-26; **(2)** the protected ribose sugar that reacts with the silylated uracil is obtained from L-ribose by treating L-ribose with methanol and acid followed by protection of the hydroxyl group with benzoyl chloride according to Reaction 1 in col. 19; and **(3)** consequently, the reaction steps of forming 1-O-alkyl-ribose by reaction of a ribose with methanol and protection of the remaining free hydroxyl groups and its coupling to uracil via the silylated derivative and subsequent deprotection of the protecting groups is taught by Gosselin *et al.* *See* pages 3-4 of the Office Action of December 28, 2007. The Examiner **has admitted** that Gosselin *et al.* does not teach that **(a)** the same reaction can be performed with a deoxyribose; and that **(b)** the 1-O-alkyl-ribose is converted to a halide before reacting it with a silylated base. *See* page 4, lines 2-5 of the Office Action of December 28, 2007.

The PTO also alleged **(1)** that Weis *et al.* teaches the reaction of a silylated base with a ribose sugar that has a chlorine at the 1-position in Scheme IV on page 13 is completed in 2 hours whereas the reaction of a silylated base with a ribose sugar that has a OAc group at the 1-position in Scheme II on page 9 is completed in 16 hours; and **(2)** that that it would have been obvious to one of ordinary skill in the art to substitute OAc with a

halide to speed up the reaction. *See* page 4, lines 6-12 of the Office Action of December 28, 2007.

The U.S. Supreme Court has recently addressed the test for obviousness under 35 U.S.C. § 103. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). In *KSR,* the Supreme Court rejected the Federal Circuit's *rigid application* of the "teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. *Id., slip op.* p. 11. According to the Supreme Court, the correct standard to apply is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). *Id., slip op.* p. 2. However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be a factor. *Id. slip op.* p. 14 ("When it first established [the TSM test], the Court...captured a helpful insight."). Indeed, on May 3, 2007, the Deputy Commissioner of Patents circulated a memorandum ("USPTO Memorandum," copy enclosed) to the Technology Center Directors pointing out that the TSM test was not completely abolished in *KSR.*

The *Graham* factual inquiries, which establish a guide for determining obviousness, are: (1) determine the scope and contents of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. *KSR, slip op.* p. 2 (*citing Graham,* 383 U.S. at 15-17).

The instant claims are not obvious in view of the cited references, Gosselin *et al.* and Weis *et al.*, because (A) the Examiner has failed to ascertain the differences between the prior art and the claims at issue; (B) the Examiner has failed to conduct the *Graham* factual inquiries properly; and (C) the cited references, individually or in combination, do not teach or suggest all the claim elements of the independent claims 13 and 17.

A) The Examiner has failed to ascertain the differences between the prior art and the claims at issue because the Examiner has failed to ascertain the differences in stereoselectivity between the deoxyriboses of the instant claims and the riboses of Gosselin *et al.* or Weis *et al.*

For a ribose having an appropriate leaving group such as a halo group at the C-1 position, the coupling reaction of the ribose with a silylated uracil derivative always provide the corresponding β nucleoside because of neighboring group participation effect (or the Baker rule) of the group at the C-2 position which is usually an acyl group. Such C-2 group

assists the leaving of the halo group at the C-1 position to form an intermediate (*i.e.*, an acyloxonium) which has the alpha face open to the incoming silylated uracil derivative to form exclusively the beta nucleoside. See the Baker Rule at lines 6-15 of page 36 of the enclosed reference by Helmut Vorbruggen and Carmen Ruh-Pohlenz, "Synthesis of Nucleosides," in "Organic Reactions," edited by Leo A. Paquette et al., John Wiley & Sons, Inc., Vol. 55, pp 35-37, (2000).

Because there is no neighboring group at the C-2 position of the deoxyriboses of the instant claims, the coupling of a silylated nucleobase such as uracil to a deoxyribose usually produces a mixture of the corresponding α and β nucleosides for the following reasons. For the coupling of a silylated uracil to a deoxyribose deoxyribose, such as step d of claim 13 or 17 of the instant application, the deoxyribose deoxyribose generally is activated with a leaving group such as halo at the C-1 position which may be in either α or β configuration. See claims 13 and 17 and lines 12-14 of paragraph [0029] of the specification. Further, the formation of the N-glycosidic bond with a displacement of the halo group generally occurs with an inversion of the α or β configuration, *i.e.*, a SN2 type reaction, which leads to the corresponding β or α nucleoside respectively. See lines 15-19 of paragraph [0029] of the specification. The halo group must have a stable α or β configuration throughout the reaction, otherwise the resulting product is usually a mixture of α and β nucleosides from which it is almost impossible to separate the isomers with methods other than chromatography. See lines 15-22 of paragraph [0029] of the specification. Unfortunately, the halo-deoxyribose in solution generally rapidly isomerizes to a mixture of α and β isomers which lead to a mixture of α and β nucleosides.

Because deoxyriboses and the riboses behave differently in stereoselectivity, therefore it is improper to combine that the teachings of deoxyriboses in Weis *et al* with the teachings of riboses in Gosselin *et al.* to reach all the claim elements of the claims of the present invention.

B) The Examiner has failed to conduct *Graham* factual inquiries properly because the Examiner has failed to determine the scope and contents of the prior art for the following reasons.

First, as mentioned earlier, the Examiner alleged that the protected ribose sugar in cols. 25-26 of Gosselin *et al.* is obtained from L-ribose by treating L-ribose with methanol and acid followed by protection of the hydroxyl group with benzoyl chloride

according to Reaction 1 in col. 19. Applicant respectfully submits that the Examiner has failed to recognize that the protected ribose sugar **143** in col. 19 is different in structure than the ribose sugar **1** in cols. 25-26. The protected ribose sugar **143** has three –OBz groups and one –OAc group whereas the ribose sugar **1** has merely two –OBz groups and two –OAc groups. The ribose sugar **1** cannot be prepared according to Reaction 1 in col. 19. Therefore, there is no factual basis for the Examiner's allegation that the reaction steps of forming 1-O-alkyl-ribose by reaction of a ribose with methanol and protection of the remaining free hydroxyl groups and its coupling to uracil via the silylated derivative and subsequent deprotection of the protecting groups is taught by Gosselin et al.

Second, as mentioned earlier, the Examiner alleged that Weis *et al.* in Scheme IV on page 13 teaches the reaction of a silylated base with a ribose sugar that has a chlorine at the 1-position is completed in 2 hours whereas the reaction of a silylated base with a ribose sugar that has a OAc group at the 1-position in Scheme II on page 9 is completed in 16 hours; and therefore, it would have been obvious to one of ordinary skill in the art to substitute OAc with a halide to speed up the reaction. Applicant respectfully submits that the Examiner has compared the wrong examples because the ribose sugar that has an OAc group on page 9 is based on **ribose** whereas the alleged "**ribose sugar**" that has a chlorine on page 13 is in fact a deoxyribose sugar based on **deoxyribose**. Further, there are **three –OBz** protecting groups in the ribose sugar on page 9 whereas there are merely **two –OTol** protecting groups in the deoxyribose sugar on page 13. Further, a skilled artisan can recognize that the extra –OBz in the 2-position of the ribose sugar on page 9 can sterically shield the 1 position of the ribose sugar from the silylated base and therefore, can slow down its reaction with the silylated base. Further, there is neighboring group participation effect in ribose sugars but not in deoxyribose sugars. Therefore, there are at least four differences between the ribose sugar and the deoxyribose sugar in addition to the difference in the leaving group at the 1 position. One of ordinary skill in the art would not have recognized which factor is actually responsible for the decrease in the reaction time. Therefore, there is no factual basis for the Examiner's allegation that it would have been obvious to one of ordinary skill in the art to substitute OAc with a halide to speed up the reaction.

C) The cited references, individually or in combination, do not teach or suggest all the claim elements of the independent claims 13 and 17, particularly step (c) of claims 13 and 17 for the following reasons. Step (c) recites "reacting the optionally protected L-1-O-alkyl-2-deoxyribose with an anhydrous acid halide to form an optionally protected L-1-halo-

2-deoxyribose, wherein the anhydrous acid halide is produced *in situ* by the reaction of an acyl halide with a sub-equivalent amount of a second alcohol."

First, the Examiner has admitted that Gosselin *et al.* does not teach the conversion of the 1-O-alkyl-ribose to a halide, such the protected L-1-halo-2-deoxyribose claimed herein, before reacting it with a silylated base. *See* page 4, lines 2-5 of the Office Action of December 28, 2007.

Second, the Examiner has admitted that Weis et al. does not teach or disclose that the acid halide in step (c) of claim 13 or 17 is produced *in situ* by the reaction of an acyl halide with an alcohol. *See* page 6-7 of the Office Action of December 28, 2007. However, the Examiner alleged that whether an acid halide is generated in situ or not, the end product is the same. Applicant respectfully submits that the Examiner's allegation is incorrect because the Examiner failed to consider many other recitations in step (c) such as (1) that the acid halide is generated from the reaction of an acyl halide with an alcohol; (2) that a sub-equivalent amount of the alcohol is used for the production of the acid halide; and (3) that the acid halide is anhydrous.

Neither Weis *et al.* nor Gosselin *et al.* discloses or suggests that the acid halide can be generated from an acyl halide. Therefore, there is no reason for a skilled artisan to use acyl halide to generate an acid halide in step (c).

Neither Weis *et al.* nor Gosselin *et al.* discloses or suggests that the acid halide can be generated from an alcohol. Therefore, there is no reason for a skilled artisan to use alcohol to generate an acid halide in step (c).

Neither Weis *et al.* nor Gosselin *et al.* discloses or suggests that a sub-equivalent amount of the alcohol can be used for the production of the acid halide. Therefore, there is no reason for a skilled artisan to use a sub-equivalent amount of the alcohol for the production of the acid halide in step (c).

Neither Weis *et al.* nor Gosselin *et al.* discloses or suggests that the acid halide is anhydrous. Therefore, there is no reason for a skilled artisan to use an anhydrous acid halide in step (c).

For the above reasons, claims 13 and 17 and thus claims 14-16, 18-20 and 69-81 and 83-85, which depends on claim 13 or 17, are therefore not obvious over Gosselin *et al.* in combination with Weis *et al.*

In view of the above comments, Applicants respectfully request withdrawal of the rejection of claims 13-20, 69-81 and 83-85 under 35 U.S.C. 103(a) as being allegedly unpatentable over Gosselin *et al.* in combination with Weis *et al.*

CONCLUSION

In light of the above amendments and remarks, the Applicants respectfully request that the PTO reconsider this application with a view towards allowance.

No fee other than the extension fee is believed due for this submission. However, if any fees are required for the entry of this paper or to avoid abandonment of this application, please charge the required fees to Jones Day Deposit Account No. 50-3013 (referencing order no. 417451-999010).

The Examiner is invited to call the undersigned attorney at (650) 739-3983, if a telephone call could help resolve any remaining items.

Respectfully submitted,

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